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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/741,550 | 12/19/2000 | Julia Y. Ljubimova | 18810-80364 | 6437 |

7590 10/19/2004

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| EXAMINER | |
|---|---|
| GOLDBERG, JEANINE ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/741,550 | LJUBIMOVA ET AL. | |
| | Examiner | Art Unit | |
| | Jeanine A Goldberg | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10,13-18,21-29,32-36,44,45,48-52,60-68 and 75-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13-18,21-29,32-36,44,45,48-52,60-68 and 75-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. This action is in response to the papers filed August 2, 2004. Currently, claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-52, 60-68, 75-78 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims and the arguments.

4. This action contains new grounds of rejection.

5. Based upon the previous comments made by the examiner, both in the office action and the interview, regarding the incorporation of a SEQ ID NO: based upon the Genbank Accession Number in the specification, it was determined that this was not appropriate. Although the examiner specifically suggested the filing of a declaration to overcome the description rejection, the response did not provide a declaration to this effect. However, the specific facts and circumstances have been more thoroughly considered with respect to the instant application and a declaration would not be appropriate means to limit the claims for the reasons presented below in the new matter rejection. The examiner sincerely apologizes for any confusion this may have caused.

6. The declaration regarding enablement of additional tumor types filed August 2, 2004 by Dr. Ljubimova has been thoroughly considered.

### *Claim Rejections - 35 USC § 112-Written Description*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-52, 60-68, 75-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to methods for detecting any malignant tumor in a human subject by comparing the expression level of laminin alpha4-specific mRNA or laminin alpha 4 subunit protein to normal controls, wherein overexpression of laminin alpha4-specific mRNA indicates the presence of a malignant tumor.

The claims are very broadly drawn to detecting a laminin alpha4-specific mRNA or laminin alpha4 subunit protein. The amendments to the claim to encompass complementary to a nucleic acid of SEQ ID NO: 1 has been noted. First, complementary does not require the full complement or even a fragment which is 100% complement of SEQ ID NO: 1. Thus the claim remains broadly drawn to aspects not described by the instant specification.

The specification specifically states that laminin alpha4 specific polynucleotide sequence include mRNA sequence at least 5-30 contiguous nucleotides long, and preferably at least about 45 contiguous nucleotides long. A laminin alpha4 specific mRNA can be but is not necessarily an mRNA species containing a nucleotide

sequence that encodes a functional laminin alpha4 subunit or a fragment thereof. Also, included among laminin alpha4 specific mRNAs are splice variants" (page 20, lines 10-20). This extremely large genus of nucleic acids has not been provided in the instant specification or the art at the time the invention was made. Further, the specification fails to provide evidence that splice-variants, mutations, homologs and other variations of the laminin alpha4 specific mRNAs are associated with malignant tumors. The art teaches mutations or splice variants in genes may significantly alter the expression patterns of genes such that they are no longer commensurate in expression with the wild type gene. It is unpredictable that the skilled artisan could use the murine homolog of laminin alpha4 to detect tumors in humans. There is no evidence that homologs would have significant homology to detect and diagnose tumors. Based upon the evidence in the specification, the declaration and the post filing date art, detection of laminin-9 does not appear to be predictably associated with tumors.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to

disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant has defined only single Genbank Accession Number provided in the art. The specification does not appear to incorporate the sequence into the specification nor does the specification appear to state that Z99289 is SEQ ID NO: 1. The Genbank Identifier Z99289 is a sequence that has been updated 3 times prior to the date of filing. Z99289.1 was first seen in NCBI on September 20, 1997. This sequence was altered on October 2, 1997, again on October 31, 1997 and again on May 30, 1998. Each of these changes was prior to the filing date of the instant application. These changes are evident based upon the mere number of base pairs in the listing. The changes have decreased over time from over 240,000bp to 190,778 bp. Thus, it is clear that the record for Genbank Accession Z99289 has changed over time. The instant specification has not described which sequence was used in the specification. Further, the Genbank sequence and SEQ ID NO: 1 is 190,778 bp in length and is directed to chromosome 6q21. There is no description or disclosure of the laminin alpha4 specific mRNA in the annotations of the sequence. It is highly likely and

most probable that additional sequences for genes and DNA are located on 6q21 which are not laminin alpha4. The claims have been amended to require "complementary to a nucleic acid of SEQ ID NO: 1." The specification has not described the sequence for laminin alpha4 specific mRNA. Thus, the claim encompasses using probes which are outside laminin alph4 for detection which does not appear to be supported by the instant specification. The specification states that gene expression microarrays have gene sequences of about 500-5000 base pairs in length. A sequence of 190,778 is clearly outside the size range discussed for the gene expression array.

Therefore, as discussed above, the very broad genus of alpha4-specifc mRNA sequences has not been described because neither the specification nor the art teaches a representative number of mutations, homologs, splice variants which are encompassed by the genus. Moreover, there is no identification of a laminin alph4 protein. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

**Response to Arguments**

The response traverses the rejection. The response asserts that "laminin alpha4-subunit has a very clear definition and one of skill in the art could readily obtain sequence information for it." This argument has been thoroughly reviewed, but is not found persuasive because the specification has not provided any guidance to the sequence of laminin alpha4. The sequence which appears to be associated with laminin alpha-4 is for chromosome 6q21 and does not recite boundaries for the alpha-4 laminin chain. Moreover, as discussed in the rejection above, complementary to a

nucleic acid of SEQ ID NO: 1 does not require that the expression for "the complement" is determined. Complementary broadly encompasses isoforms, splice variants, homologs and additional sequence which have not been described by the instant specification. Thus for the reasons above and those already of record, the rejection is modified and maintained.

***Claim Rejections - 35 USC § 112- Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-52, 60-68, 75-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to methods for detecting any malignant tumor in a human subject by comparing the expression level of laminin alpha4-specific mRNA complenetary to a nucleic acid of SEQ ID NO: 1 or laminin alph4 protein to normal controls, wherein overexpression of laminin alpha4-specific mRNA or protein indicates the presence of a malignant tumor.

The art, namely Ringelmann et al. (Experimental Cell Research, Vol. 246, pages 165-182, 1999) teaches strong interstitial expression of laminin alpha4 mRNA in

myogenic tissues of embryonic but not mature mice, implicating a role for this laminin alpha chain in myogenesis (page 166, col. 2). Additionally, Previtali et al. (Glia, Vol. 26, pages 55-63, 1999) teaches the abnormal expression of a laminin receptor, alpha6beta4 integrin in human astrocytomas (abstract). Tysnes et al. (Int. J. Devl. Neuroscience, Vol. 17, No. 5-6, pages 531-539, 1999) teaches "compared to normal astrocytes, neoplastic astrocytes in situ have shown increased expression of the laminin receptor alpha3 and beta1 integrin subunits" (page 538).

Ljubimova et al. (Cancer Research, Vol. 61, No. 14, pp 5601-5610, July 2001) teaches that laminin-8 and laminin-9 have different effects on the recurrence of tumors. Thus, it is clear that mere detection of alpha4, without more does not accurately provide an analysis of recurrence rates.

The claims are very broadly drawn to detecting a laminin alpha4-specific mRNA. The specification specifically states that laminin alpha4 specific polynucleotide sequence include mRNA sequence at least 5-30 contiguous nucleotides long, and preferably at least about 45 contiguous nucleotides long. A laminin alpha4 specific mRNA can be but is not necessarily an mRNA species containing a nucleotide sequence that encodes a functional laminin alpha4 subunit or a fragment thereof. Also, included among laminin alpha4 specific mRNAs are splice variants" (page 20, lines 10-20). This extremely large genus of nucleic acids has not been provided in the instant specification or the art at the time the invention was made. Further, the specification fails to provide evidence that splice-variants, mutations, homologs and other variations of the laminin alpha4 specific mRNAs are associated with malignant tumors. The art

teaches mutations or splice variants in genes may significantly alter the expression patterns of genes such that they are no longer commensurate in expression with the wild type gene. It is unpredictable that the skilled artisan could use the murine homolog of laminin alpha4 to detect tumors in humans. There is no evidence that homologs would have significant homology to detect and diagnose tumors.

In the instant case, Applicant has defined only single Genbank Accession Number provided in the art. The specification does not appear to incorporate the sequence into the specification nor does the specification appear to state that Z99289 is SEQ ID NO: 1. The Genbank Identifier Z99289 is a sequence that has been updated 3 times prior to the date of filing. Z99289.1 was first seen in NCBI on September 20, 1997. This sequence was altered on October 2, 1997, again on October 31, 1997 and again on May 30, 1998. Each of these changes was prior to the filing date of the instant application. These changes are evident based upon the mere number of base pairs in the listing. The changes have decreased over time from over 240,000bp to 190,778 bp. Thus, it is clear that the record for Genbank Accession Z99289 has changed over time. The instant specification has not described which sequence was used in the specification. Further, the Genbank sequence and SEQ ID NO: 1 is 190,778 bp in length and is directed to chromosome 6q21. There is no description or disclosure of the laminin alpha4 specific mRNA in the annotations of the sequence. It is highly likely and most probable that additional sequences for genes and DNA are located on 6q21 which are not laminin alpha4. The claims have been amended to require "complementary to a nucleic acid of SEQ ID NO: 1." The specification has not described the sequence for

laminin alpha4 specific mRNA. Thus, the claim encompasses using probes which are outside laminin alph4 for detection which does not appear to be supported by the instant specification. The specification states that gene expression microarrays have gene sequences of about 500-5000 base pairs in length. A sequence of 190,778 is clearly outside the size range discussed for the gene expression array.

Based upon the evidence in the specification, the declaration and the post filing date art, detection of laminin-9 does not appear to be predictably associated with tumors. Laminin-9 comprises the alpha-4 subunit.

With respect to Claims 28-29, 32-36, 44-45, 48-52 the post filing date are suggests that laminin-8 which was expressed mainly in blood vessel walls of GBMs and histologically normal tissues adjacent to GBMs had a shorter mean time to recurrence. Whereas laminin-9 which was expressed mainly in blood vessel walls of low-grad tumors and normal brain, had a greater time to tumor recurrence. Moreover, the specification, on pages 44-54 discuss Patient 16 and 39 and the relative recurrence rates. It is noted that claims 44 and 53 are sufficiently identical.

With respect to Claims 60-66 directed to method of classifying the grade of a malignant tumor by comparing expression profiles, the specification has provided no guidance to classification. The specification has provided no guidance as to what the "relatively high invasiveness of the tumor" encompasses. The specification seems to illustrate a few examples where laminin alpha4 is overexpressed in astrocytoma grade II. The specification teaches that astrocytoma grade II is a lower grade malignant tumor (page 11, lines 15-16). Therefore, it is unclear how the overexpression of laminin is

indicative of relatively high invasiveness of the tumor. The claims does not appear to make any distinction between low grade and higher grade tumors. Therefore, it is unclear how the tumors are classified. While the skilled artisan could provide further undue experimentation to determine a value for expression in the various types of tumors and obtain thresholds for classifying the tumors, the instant specification does not provide any predictive correlation between thresholds and classifications of tumors into grades, as required by the claims.

Moreover, the specification provides no guidance to the skilled artisan how to use the invention with respect to any type of malignant tumor. The specification does not teach expression levels in all malignant tumors, including breast, prostate, lung, colon, skin, etc. While one could conduct additional experimentation to determine whether, e.g., overexpression of laminin alpha4 might be associated with, e.g., additional malignant tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references, do not provide support for the use of laminin alpha4 expression as an indicator of malignant tumor. Thus it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between laminin alpha4 expression and malignant tumors, it is further unpredictable as to whether any quantity of

experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

**Response to Arguments and Declaration**

The response traverses the rejection.

First, the rejection has been changed from a scope of enablement to an enablement rejection since the insertion of SEQ ID NO: 1 would constitute new matter and the examiner can not suggest another means for claiming the laminin alph4-specific mRNA based upon the lack of teachings in the specification and the very broad definition in the specification. Thus, the instant rejection is no longer direct to a scope of enablement, but rather a lack of enablement.

As discussed previously, the Declaration filed March 17, 2003, states that "like brain malignancies, malignant tumors of the breast over expresses alpha4 laminin." (page 2 of Declaration filed March 24, 2003). The specification makes clear that the laminin alpha4 subunit is particular to laminin-8, laminin-9 and laminin-14 (page 5, lines 17-19). The data in the Declaration illustrates that Laminin-8 is not expressed in normal tissue, but appears expressed in invasive carcinoma, metastases of invasive carcinoma and non-invasive carcinomas. However, Laminin-9 does not appear to be correlative of the same expression pattern. Laminin-9 is expressed in normal breast tissue (40%). This appears to indicate that the alpha4 subunit may not be responsible for the expression in breast tissues. The response argues on page 23 of the Response that "Laminin 8 requires an overexpression of both alpha4 and beta1 subunits." Therefore,

the expression of Laminin 8 in breast, but not in normal may be due to the beta1 subunits since Laminin 9 does not have the same correlation.

The response asserts that the declarations clearly show that the invention is readily applicable to breast cancer as well as brain cancer (page 21 of response). This argument has been thoroughly reviewed, but is not found persuasive because the first Declaration illustrates the expression of brain metastasis of breast cancer. As stated in the prior office action, "with regard to the data presented on Page 4 of the Declaration, the western blot appears to show a lack of laminin alpha4 chain expression in normal breast tissue and its strong expression in breast cancer metastases. The Figure illustrates that the metastasis are "brain metastasis of breast cancer." Therefore, the results of the Figure appear to support a brain metastasis of breast cancer, but does not support breast cancer malignancies.

Discussion of 132 Declaration filed July 28, 2004: The declaration states that the results for malignant breast tumors are very similar to those for malignant brain tumors, but the picture is more complex because of tissue types. The declaration states that there is some alpha4 laminin expression in normal ductal tissue but not in normal breast vasculature. This statement does not appear to support that the skilled artisan would be able to take any tissue type, as instantly claimed to determine and compare expression levels to indicate tumors. The response states that 45 human breast tissue samples were used, however only 8 samples are illustrated in the declaration.

The declaration (para 10) discusses the importance of the beta1 or beta2 expression. It is noted that this is not a limitation of Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-52, 60-68. The MPEP requires that "a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." Here the declaration appears to be illustrating that beta1 and alph4 (i.e. laminin-8) is essential to determining tumor status and can not be based upon alph4 alone. Specifically, the declaration discusses that "occasional strong expression of alpha4 in normal tissue correspond to laminin-9 but not Ln-8." Thus, the alpha4 nucleic appears to be only be informative when expressed with beta1. The declaration superficially states that "to take the expression of laph4 and beta2 into consideration, the expression pattern of the combination with alpha4 and beta1 is more predominant in cancerous tissues than normal tissues.

Analysis of Figure 1 illustrates that 50% of the normal tissues illustrated demonstrated a high expression of laminin alpha4. It is clear that in the primary invasive ductal cancers, laminin alpha 4 is not overexpressed as compared to "normal 2." Thus, to compare the expression of alpha4 subunit to normals would not provide reliable and predictable results.

Table 1 of the declaration is directed to the colocalization of alpha4 and beta1. This data further appears to support that the alpha4 chain does not provide significant and sufficient information to determine tumor status.

The response asserts that there is no possibility of mistaking breast cancer for brain cancer because all of these samples are analyzed histologically and the tissue

differences between breast cancer and brain cancer are unmistakable. This argument has been thoroughly reviewed, but is not found persuasive because the claims are drawn to determining the type of cancer. The claims are drawn to determining whether the tissue has a tumor based upon the overexpression of alpha 4. The claims do not rely upon histological examination.

The response asserts that preliminary data for prostate cancer suggests that only relatively non-invasive prostate cancers have been evaluated. Based upon the interview, the applicant suggested that in the three prostate tumors were sampled and no alpha4 expression was found. Thus, the assertions by the applicant that all cancers overexpress laminin alpha4, does not appear to be consistent with the data provided in the specification, the art and the interviews. It is unpredictable whether additional experiment would enable the skilled artisan how to practice the claimed invention over the full scope of the claims. As stated previously, while one could conduct additional experimentation to determine whether, e.g., overexpression of laminin alpha4 might be associated with, e.g., additional malignant tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue." It is well established that different cancers have expression of different genes. Thus, there is no indication that breast cancer, or any other cancer, has increased expression of alpha4 chain compared to normals, as laminin lapha4 is highly expressed in normal2. The response appears to support this conclusion by asserting that "very high levels of alpha4 and the presence of laminin 8 are markers for an aggressive tumor that has a very high potential for metastasis." Thus, the evidence provided in the

declaration may support that metastasized tumors from the brain also show an increased level of alpha4, however they do not illustrate that alpha4 is overexpressed in breast cancer.

With respect to Claims 60-66, the response argues that directed to method of classifying the grade of a malignant tumor by comparing expression profiles, the specification has provided no guidance to classification. The response (page 24 of response filed November 17, 2003) asserts that traditional ranking or grading of tumors is based strictly on histological features but histological features were unable to correctly identify aggressiveness and tendency to recur. The Examiner pointed out several points of confusion and the response asserted that this was exactly the point. However, there is no evidence that the expression patterns provide a more accurate measurement than the art established histological methods which have existed for many years and are well established. The method merely describes a generic method for assessing grades such that the higher the expression the higher the grade. The response appears to be arguing that the instant application has determined a system that "is intended to replace the traditional histological grading or ranking." This aspect of the instant invention does not appear to have been fully developed. It is noted that overexpression in particular tissues may be indicative of tumors, however there is no apparent thresholds for assigning any particular rank. In the event that overexpression of 2x as compared to normal is ascertained, there is no guidance as to what rank or grade tumor is found. The specification does not appear to establish any ranking system, any system for tumor aggressiveness. There are not specifics in the

description what various grades of tumors encompass. Therefore, the skilled artisan would not be able to establish the specific grade of a tumor with out further experimentation.

Thus for the reasons above and those already of record, the rejection is maintained.

***New Matter***

9. Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-52, 60-68, 75-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to require "complementary to a nucleic acid of SEQ ID NO: 1." The specification provides in Table 3- Expression of structural genes. The gene name s provided as laminin alph4 chain and Genbank accession Number Z99289.

The examiner acknowledges that in the interview summary she indicated that it was her understanding that to bring in a Genbank Accession Number into the specification/claims, a declaration would be appropriate to establish that at the time of invention the Genbank Accession Number was a particular sequence, amend the Sequence listings and specification. The issue has become more involved based upon the response filed for the reasons which follow.

First, the sequence provided in the specification has been updated 3 times prior to the date of filing. Z99289.1 was first seen in NCBI on September 20, 1997. This sequence was altered on October 2, 1997, again on October 31, 1997 and again on May 30, 1998. Each of these changes was prior to the filing date of the instant application. These changes are evident based upon the mere number of base pairs in the listing. The changes have decreased over time from over 240,000bp to 190,778 bp. Thus, it is clear that the record for Genbank Accession Z99289 has changed over time. The instant specification has not provided any guidance as to which sequence was used in the specification. Thus, it is new matter to bring in one of these particular 4 sequences without some support.

Second, the Genbank sequence and SEQ ID NO: 1 is 190,778 bp in length and is directed to chromosome 6q21. There is no description or disclosure of the laminin alpha4 specific mRNA in the annotations of the sequence. It is highly likely and most probable that additional sequences for genes and DNA are located on 6q21 which are not laminin alpha4. The claims have been amended to require "complementary to a nucleic acid of SEQ ID NO: 1." Thus, the claim encompasses using probes which are outside laminin alph4 for detection which does not appear to be supported by the instant specification. The specification states that gene expression microarrays have gene sequences of about 500-5000 base pairs in length. A sequence of 190,778 is clearly outside the size range discussed for the gene expression array.

Finally, the instant specification appears to merely reference the Genbank Accession number. MPEP 608.01 (p) states "mere reference to another application,

patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973)." The MPEP further states "The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973)." The MPEP thus appears to only allow for incorporation of essential material if it was incorporated by reference, which does not appear to be the case here.

Therefore the inclusion of "complementary to a nucleic acid of SEQ ID NO: 1" constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

***Conclusion***

**10. No claims allowable.**

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

**Jeanine Goldberg**
**Patent Examiner**
October 15, 2004